Exciting matters in electroconvulsive therapy : studies on seizure thresholds

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Introduction

Electroconvulsive therapy offers exciting subject matters for the human brain, clinicians and scientists

"Het was alsof ze feestvierde op den bodem van een diepen put,
waaruit nooit iemand verlost werd. Soms dacht zij, dat dit op de hel leek,
waar de verdoemden het laatste oordeel afwachten en zich verdooven door
feestgedruisch in kunstlicht, daar Gods zon hun niet meer gegund is."

Frederik van Eeden, Van de koele meren des doods, 1900.

"It was as if they were celebrating at the bottom of a deep well,
from which no person would ever be redeemed.
Sometimes she thought that this resembled hell,
where the doomed await their final verdict and benumb themselves by feasting
in artificial light, as they are no longer blessed with God's sun."

Frederik van Eeden, The Cool Lakes of Death, 1900.

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"Depressie gaat nergens over; het is een lege archiefkast.
Ik heb eindeloos gezocht naar een oorzaak van mijn somberheid,
maar ik kom er gewoon niet achter."

Mike Boddé, Pil, 2010.

"Depression deals with nothing; it is an empty filing cabinet.
I have searched endlessly for a cause of my sorrow,
but I just can't understand it."

Mike Boddé, Pill, 2010.

The suffering of depressed patients is enormous. It also poses an important burden on their significant others and on society as a whole. Clinicians are therefore being urged to relieve these conditions as soon as possible. To that purpose, effective psychotherapeutic, psychopharmacologic and other biological interventions, such as electroconvulsive therapy (ECT), are available. Observing a quick response to a course of ECT in a psychotic depressed patient is astonishing. ECT may restore the patient's normal mood, but at the same time may provoke anxiety and a sense of shame or stigmatization. Frequently, ECT is accompanied by more or less impairing cognitive side effects.

For clinicians and scientists, ECT is fascinating and raises many research questions concerning the effects of this treatment on the functioning of the brain. This thesis reports on our daily practice in which we treat severely ill depressed patients, while simultaneously doing clinical research. To further improve the understanding and the effectiveness of ECT, the electrical dose, which elicits the seizure activity (defined as seizure threshold [ST]), is the subject of this thesis.

1. Clinical aspects of ECT

1.1 Indications for and use of ECT in the Netherlands

In the Netherlands, the use of ECT is limited, functioning mostly as the 'treatment-of-last-resort' for severely ill patients suffering from (psychotic and/or pharmacotherapy resistant) depression, mania, intractable psychosis, catatonia, neuroleptic malignant syndrome, or delirium.[1,2] Worldwide, it has been estimated that approximately 1 million patients receive ECT each year.[3] As the incidence of major depressive disorder with psychotic features (an important indication for ECT) is about 4 in 1,000 individuals in the general population,[4] an incidence rate of about 64,000 patients might be expected in the Netherlands annually. This number contrasts greatly with the actual amount: in 1999 only 328 Dutch patients received ECT.[5] Nevertheless, ECT is a very effective biological treatment. Bilateral (BL) ECT is moderately more effective than right unilateral (RUL) ECT and high dosed ECT more effective than low dosed.[6] In adults with a major depressive disorder, ECT is probably more effective than pharmacotherapy.[6] It is also possible that certain depressed patients such as psychotic, catatonic, suicidal or otherwise life threatened patients may benefit even more from ECT than others.[1]

In the Netherlands, it is mostly general and university hospitals that provide ECT. The procedure follows the clinical guidelines of the Netherlands Association of Psychiatry ('NVvP') on the practice of ECT.[7,8] In 2010, references in the Dutch

national register for treatments ('Diagnose-Behandelcombinatie Informatie Systeem') revealed that ECT courses were given with a median of 9 sessions (interquartile range 4-15 sessions). The majority - female patients (75%) with an average age of 58 ± 15 years - were treated because of recurrent mood disorders (85%), often with psychotic features (33%).[9] Although most psychiatric patients are diagnosed and treated for their psychiatric illnesses in facilities for mental health care ('GGZ-instellingen'), only a minority of these institutions offer ECT. The annual use of ECT in the Netherlands had increased substantially from 1.8 per 10,000 inhabitants in 1999[5] to 8.5 per 10,000 inhabitants in 2008.[8] However, this rate is still low compared with the 14 treatments per 10,000 inhabitants in Scotland[10] and the approximately 27 per 10,000 inhabitants in the USA.[3]

1.2 Clinical practice of ECT

To be effective, ECT must induce generalized seizure activity in the brain of the patient by overcoming the ST.[11] Effectiveness of ECT not only depends on the administered electrical stimulus and the induced seizure, but is also related to electrode placement, level of seizure generalization and the extent to which the ST is exceeded.[1] Seizures are elicited by an electrical stimulus that is administered between two electrodes placed at the outside of the patient's head. In the Netherlands, ECT is usually given twice a week,[8] and takes place under general anesthesia in order to prevent awareness and distress. The patient also receives a muscle relaxant to prevent complications such as injuries and fractures.[1,7]

Generalized seizure activity occurs only when the electrical stimulus is strong enough to exceed a critical threshold (i.e., the ST).[12] The ST has several definitions in the literature. Normally, the smallest electrical stimulus dose that is necessary to produce a generalized seizure of at least 25-30 seconds on electroencephalogram (EEG)[1,13] is defined as the initial seizure threshold (IST). This definition seems arbitrary, however. Whether there are associations between the level of the ST and seizure duration on the one hand and the clinical effectiveness of ECT on the other hand is still a matter of debate. Moreover, experimental data to support the universally recommended 25-30 second minimum duration on EEG to define ST is lacking.[1,14] Although not studied extensively, for decades it has been clinically known that the level of IST varies substantially among patients.[14] Besides the anesthetic used, several other factors were described to affect the level of IST including gender,[15] age,[15,16] previous ECT treatment and concomitant medication use.[1,17] Additionally, ST seems to increase during the course of ECT, at least in some patients.[15,18] Recently however, this finding was not confirmed in BL ECT.[19] Underlying mechanisms explaining the initial ST level and its possible increase are hypothetical and need further study.

1.3 Optimal exceeding of the ST

For the individual patient, knowledge of the IST level seems crucial for estimating the proper electrical dose.[20,21] It is well-known that in RUL ECT the electrical dose should exceed the IST substantially (e.g., 6-12 times) to be as effective as BL ECT, with the advantage that RUL ECT results in fewer cognitive adverse effects than BL ECT.[22] Among ECT practitioners however, controversy exists about the optimal suprathreshold electrical stimulus dose and its proper determination.[14,23] Furthermore, it has been reported that the extent of the electrical dose above the individual IST, rather than the absolute electrical dose, was associated with short-term cognitive adverse effects.[20] Conversely, attempting to administer the lowest possible dose bears the risk of a subconvulsive stimulus and consequently of severe bradycardia and asystole.[24]

To decide on the proper electrical dose for a patient, the 'empirical dose-titration method' is used to calculate individualized stimulation above ST.[25] This means that, under proper anesthesia and muscle relaxation, the brain is initially stimulated with a low electrical stimulus; if consequently no seizure of a certain duration occurs, re-stimulation of the brain follows according to the steps of a predefined titration protocol. Also, in clinical practice, 'age-based' methods are often used to estimate the electrical dose that exceeds the ST sufficiently,[14,26] based on the assumption that increasing age raises the ST.[2] Furthermore, a 'fixed-high dose' strategy has been described in which a high dose (i.e., 400 milliCoulombs) is always administered regardless of other factors. This procedure may probably lead to overdosing in a substantial number of patients and a higher rate of cognitive adverse effects.[1]

In the literature, discussion exists about the accuracy of determining the IST using titration protocols.[27] It was suggested that only one single pulse of electrical current can decrease the ST, which may lead to underestimation of the IST with each additional stimulus administered during the titration procedure itself.[28] Also, most titration protocols vary regarding the used pulse widths, charge rates and increments of stimulus dosage causing internal inconsistency of the titration methods.[27] Therefore, studying the various factors that may determine the individual ST and its relation to the effectiveness and adverse effects of ECT in more detail is warranted.

Before focusing on the possible determinants of the ST, some understanding of the basic mechanisms of normal brain functioning, as described below, is helpful.

2. Normal human brain functioning

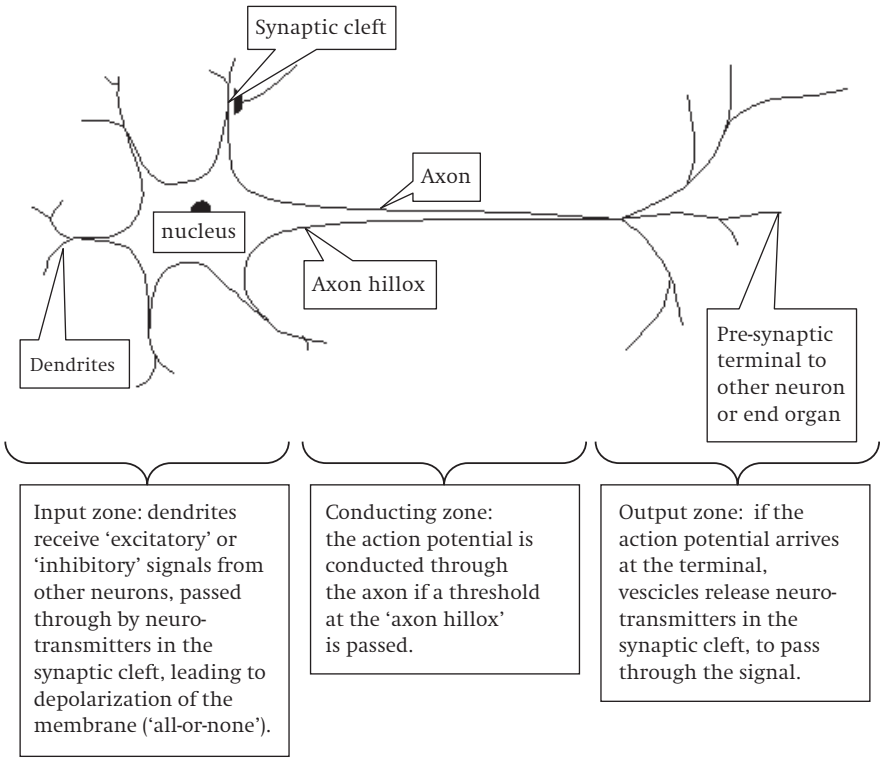
2.1 Communication systems and signaling in the brain

Most of the human brain's functions are based on the coordinated electrical and chemical interactions of large numbers of neurons that are distributed within and across different specialized brain areas (neuronal networks).[29] Ordinarily, using their sodium-potassium exchange pump, neurons generate a negative resting membrane potential and employ several different types of electrical signals to encode and transfer information. Neurons have cell bodies ('the soma') with dendrites and an axon (see Figure 1). Neuronal membranes may become more depolarized (becoming less negatively charged) by the influx of positively charged sodium ions. This depolarization occurs locally and propagates. Consequently, excitation of the membrane spreads from dendrites (input zone of the neuron), through the membrane of the cell body, towards the axon hillox. If at the hillox a critical threshold of sufficient depolarization has been reached, an action potential, following an 'all-or-none' excitatory process, is sent down the axon (conducting zone) and passed on to the dendrites of other neurons or end organs (output zone). All together, around 100 billion neurons communicate with each other through electrical and chemical signals.

When the action potential reaches the terminals of the neurons, calcium channels are opened leading to the release of neurotransmitters from the presynaptic neuron into the synaptic cleft (chemical synapse). These neurotransmitters (such as the excitatory glutamate or inhibitory gamma-aminobutyric acid [GABA]) attach to receptors at the dendrites of postsynaptic neurons. This causes the opening of sodium and other channels, which results in either continued depolarization of these dendrites or termination of the signal. As a result, the chemical signals may be excitatory (leading to depolarization of receiving neurons) or inhibitory (leading to hyperpolarization). Besides this chemical synaptic signaling, gap junctions (places of intimate contact between neurons) serve as electrical synapses passing through the current directly between neurons.[30] This direct electrical signaling is extraordinarily fast and such synapses may interconnect many neurons, facilitating synchronization among populations of neurons.

Glia cells, known as 'white matter' (astrocytes, microglia cells, oligodendrocytes), which surround the neuronal axons, seem to be particularly important in maintaining electrical and chemical balance as well as setting the general tone of excitability in the brain.[31] Glia cells can release or absorb glutamate and therefore excite or depress neurons.[31] Glia cells cannot generate electrical impulses themselves and seem to communicate with each other through calcium signaling.

Figure 1 The neuron consists of a cell body with nucleus (soma), dendrites and an axon (which starts with the 'axon hillox')



Glia cells do sense, affect and respond to changes in voltage as they absorb potassium ions released by neurons, drain these ions away into the bloodstream, and maintain proper potassium concentrations outside the neurons. These processes also lead to electrical charging and discharging throughout the brain.

All together, very efficient and huge communication systems within the brain exist, which are disrupted when a patient has a seizure. Knowledge about the generation of seizure activity, its spreading through the brain and its termination is important for our understanding of how ECT may work.

2.2 Network dynamics in the brain

In seizure activity, as provoked by ECT, the normal network dynamics of the brain are disturbed. Normal activity of large populations of neurons, working together in huge neuronal networks, is essential for optimal brain functioning. Even in the

absence of environmental and body-derived stimuli (resting state), the brain is perpetually active. In the human brain, most of the 100 billion (10^{11}) neurons are connected locally and approximately 100-200 million axons serve to interconnect symmetric and asymmetric neuronal groups in the two hemispheres, forming the corpus callosum and the somewhat larger numbers of long-range fibers connect areas within the same hemispheres.[32] Because of this tremendous connectivity and in order to generate a harmonious interplay between cortical circuits, excitation of neurons must be balanced with an equally effective inhibition so that neuronal homeostasis can be reached. Therefore, a stabilizing internal negative feedback control system is needed.[32,33] This neuronal homeostasis is often accomplished by oscillations, maintained by connected interneurons which use GABA-ergic neurotransmission and electrical gap junctions to stabilize the (local) networks.[32,34] Phenomena of neural network destabilization during seizure occurrence and propagation, as well as the network stabilization mechanisms, are most likely important in ECT and may partly determine the ST.

3. Technical aspects of ECT

3.1 Seizure generation and propagation

In the case of generalized seizure activity, overly large populations of neurons become excited simultaneously (known as synchronization) and are insufficiently compensated by inhibitory interneuron systems. As neurons are anatomically connected in neuronal networks (e.g., through cortico-cortical and cortico-thalamo-cortical feedback loops), during the process of synchronization, progressive recruitment (known as coupling) of different connected brain areas precedes complete system destabilization, clinically known as generalized seizure activity.[33,35] Seizures then result from large neuronal firing in pathological synchrony superimposed on the background activity, which disrupts normal brain function.[33,34,36,37] Seizure activity appears not only to be a neuronal process and glia cells also seem to play an important role.[31] During seizure activity, glia cells may release glutamate and other substances which may intensify the excitability of neurons, like pouring fuel on a fire.[31] Furthermore, glia cells may stimulate synapses connecting neurons into circuits by releasing growth factors in response to seizure activity.[31]

Seizure activity does not spread diffusely throughout the brain, but propagates along specific anatomic pathways.[38] For example, the hippocampus is often one of the first regions to exhibit seizure activity because of its apparently low ST, and basal ganglia circuits are suggested to control cortical excitability and to regulate

synchronization of neuronal discharge in widespread regions of the cortex.[38] Cortico-cortical seizure propagation between the frontal and parietal association cortex, with little effect on the intervening cortical regions, may occur through long association fiber pathways such as the superior longitudinal fasciculus.[39]

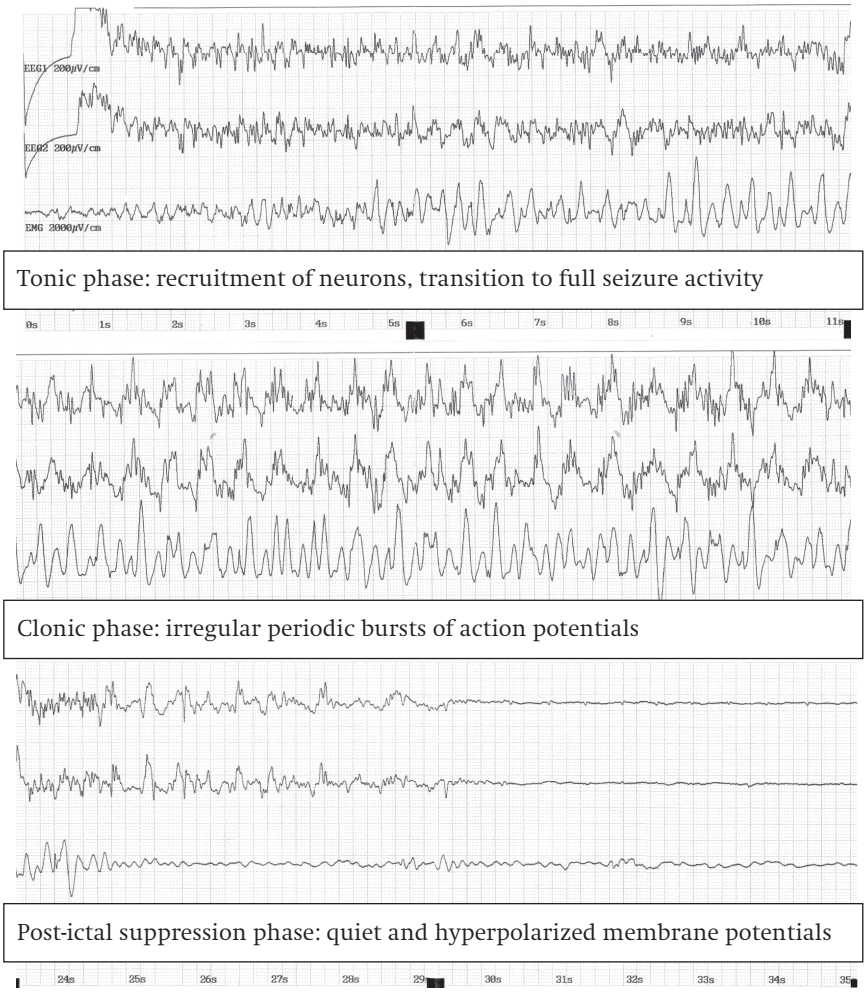
It can be hypothesized that, on the one hand, the amount of neuronal and glial connections will (at least partly) determine whether or not seizure activity will propagate through certain parts of the brain. On the other hand, a certain amount of connections would contribute to negative feedback systems and inhibition of (locally induced) seizure activity. In ECT, eliciting widespread seizure activity by exceeding the ST is intended. Therefore, externally administered electrical stimuli must induce a critical amount of synchronization in both large and connected brain areas, and must also overcome the inhibitory feed-back systems.

3.2 Seizure induction and termination in ECT

Traditionally, direct electrical depolarization of large groups of neurons by the flow of negatively charged electrons between two ECT electrodes has been described as the mechanism for seizure generation in ECT. Recently, it was proposed that electrical stimulus pulses pass through neuronal cell membranes and interact with the operation of the sodium-potassium exchange pump across it. Presumably, with each ECT stimulus pulse the intracellular sodium levels increase, leading to neuronal depolarization. As these depolarized neurons depolarize adjacent neurons, a wave of depolarization consequently sweeps through the brain, known as seizure activity.[28,30] In ECT, the transition to a fully generalized seizure is associated with maintained depolarization of the membrane potential and repetitive generation of action potentials (resulting in the clinically visible muscle spasm known as the tonic phase), followed by a period of irregular periodic bursts of action potentials (resulting in the clinically visible muscle contractions known as the clonic phase). With the final phase, the seizure ends with a relatively quiet and hyperpolarized membrane potential corresponding to a period known as post-ictal suppression.[36] These three phases can be identified on the EEG during ECT (Figure 2).

Passing through the scalp, skull, meninges and cerebrospinal fluid (CSF) space, electrical stimulation leads to a local sphere of depolarized neurons beneath the ECT electrodes, which increases in size with more electrical current. The pattern of propagation of activated neurons is likely to reflect the pattern in which axons project through the cortex, i.e., the cortico-(thalamo-)cortical networks.[40] Old cadaver studies using intracranial probes estimated that only 10% of the electrical current applied to the head reaches the brain tissue. Furthermore, the current did

Figure 2 Electroencephalographic registration of seizure activity during electroconvulsive therapy



not concentrate in one area or pathway, although with BL electrode placement the voltage was higher in the frontal lobes. Also, the current traversed the gray matter (soma and dendrites of neurons) relatively freely, but in white matter (axons surrounded by glia cells) the current generally followed the direction of the axons, concentrating in structures such as the corpus callosum, and traversing both sides of the brain, even when one electrode was applied to the vertex and the other to the parietal region (in clinical practice: placement according to d'Elia).[41,42]

More recently, single-photon emission computed tomography (SPECT) showed that BL electrode placement focally and bilaterally activated the frontotemporal and parietal association cortex, without affecting other brain regions; whereas in RUL ECT the left frontotemporal region remained relatively unaffected.[43] In another SPECT study, increase of cerebral blood flow at induction of the ECT seizure was shown near the electrodes as well as in some thalamic and basal ganglia regions. During the seizure, thirty seconds later an increase of blood flow occurred mainly in the parietal and occipital lobes. These phenomena were suggested to reflect seizure propagation through cortico-cortical (between the frontal and parietal association cortex) and cortico-thalamo-cortical (descending connections from frontal cortex to thalamus) networks.[39]

After seizure induction and propagation, ECT or the seizure itself activates mechanisms to terminate seizure activity and to create a period of post-ictal suppression. Seizure termination is unlikely to be caused by neuronal exhaustion or lack of metabolic substrate, but is probably the result of enhancement of the GABA-ergic neurotransmission during the ECT course.[12] Ten minutes after one single ECT-session, a huge increase in serum GABA levels was shown, suggesting an acute inhibitory GABA-ergic response to ECT and/or seizure activity,[44] although another small study found the opposite.[45] Based on results from human and animal studies, in the literature, a "network inhibition hypothesis" for epilepsy was proposed. An increased cortical activity in one region might inhibit subcortical arousal systems, which might lead to widespread decreased cortical activity.[46] In the post-ictal period, it was further observed that activity in the cerebellum continued to increase before returning to baseline. This might suggest inhibitory outputs from cerebellar Purkinje cells, influencing thalamico-cortical circuits that might contribute to seizure termination and/or post-ictal suppression in epilepsy,[46] and possibly also in ECT.

It is suggested that generalized and repeated seizures that terminate themselves and affect, in particular, prefrontal regions and thalamic structures, are essential for the efficacy of ECT.[28] It is likely that the mechanisms through which seizures cure patients involve structural and functional changes at different levels of complexity in the human brain. A course of ECT may restore more balanced neuronal activity and may reorganize preexisting brain homeostasis.[28] It is still a mystery as to which mechanisms are specifically responsible for the therapeutic effectiveness of ECT. For clinicians however, it is very important to apply an optimal beneficial electrical stimulus that will elicit a therapeutic and self-limiting seizure in the patient. In daily practice, there are some factors that have been supposed to obstruct optimal seizure induction, propagation and termination, and these determinants are subject to further studies.

4. Challenges for ECT

4.1 Obstacles in seizure induction

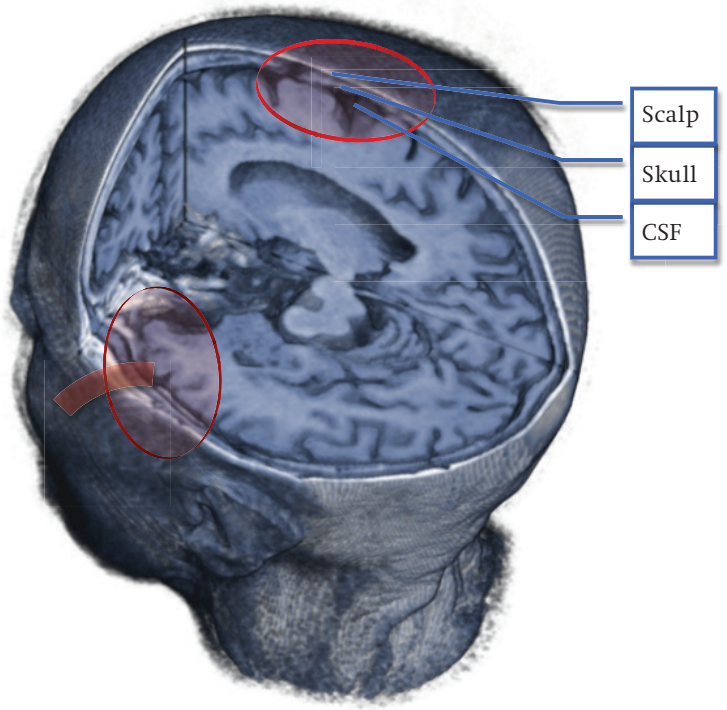
To reach the brain tissue effectively, the electrical stimulus must successively pass scalp tissue, skull, meninges, and cerebrospinal fluid (CSF), with each compartment (Figure 3) having a typical resistance to the passage of the stimulus.[47] Because the human skull is highly resistant to the passage of electrical current, large-voltage electrical stimulation must be applied to the scalp. Most of the flow of electrons is lost even before it reaches the brain tissue. After passage through scalp, skull and dura mater, the next layer consisting of CSF (an excellent conductor) also shunts current away from the brain tissue. A recent computerized simulation study of ECT in spherical head models estimated large effects of the variations in scalp and skull thickness as well as in brain volume, on the levels of stimulation strength and excited brain volume underneath the electrodes.[47] The amount of bone tissue and CSF in an individual patient, therefore, determines the amount of current reaching the brain tissue.[48] Moreover, the amount of shunting of the current depends on the distance between the two electrodes and the use of conducting substances (gel, saline, but also hairspray). The clinician modulates this distance between the two electrodes by choosing the electrode placement (BL[2], bifrontal[1] or RUL placement according to d'Elia[49]).

Interestingly, it is not common practice to evaluate skull and brain anatomy in patients undergoing ECT in order to decide on optimal electrode placement and electrical dosage. In older literature it was shown that the current density in the cortex immediately underneath sutures (places where the bony plates of the skull attach) may be three times higher than predicted.[50] This suggests the possible importance of assessing at least some of these anatomical features in the patient.

4.2 Obstacles in seizure propagation and termination

In ECT, seizure activity propagates through different parts of the brain following neuronal circuitry.[39] This process is followed by seizure termination probably induced by inhibitory thalamico-cortical feedback circuits and GABA-ergic enhancement.[44,46] Disease-related alterations of these anatomical connections and neurotransmitter systems may also interfere directly with mechanisms that support neuronal synchronization, seizure spreading and termination. For example, ischemic injuries of brain tissue, such as white matter hyperintensities, might cause certain cortico-(thalamo-)cortical circuits to be disconnected.[51] In the literature, ECT has been described to be less effective in older patients who showed more subcortical gray matter hyperintensities on MRI and medial temporal lobe atrophy.[52,53] Therefore, more destruction of connected neuronal circuits may lead

Figure 3 A T_1-weighted magnetic resonance imaging of the head to illustrate that the electrical stimulus must successively pass scalp tissue, skull, meninges, and cerebrospinal fluid (CSF), with each compartment having a typical resistance to the passage of the stimulus*



*Electrodes are shown in red and placed according to d' Elia and bifrontotemporal left. During electrical stimulation, the most electrons will flow between the two electrodes through the scalp without crossing the skull. Electrons that pass the highly resistant skull will reach the meninges and CSF space and will then be shunted between the electrodes due to the very low resistance of CSF. Therefore, only a small portion of the electrical current will excite the brain tissues and will be able to elicit seizure activity. Moreover, in right unilateral electrode placement, most current will excite the anterior two-third of the cortex ipsilateral to the electrodes, and in bifrontotemporal electrode placement the anterior frontal part of the brain tissue will be excited.

to less seizure propagation and/or less integrity of terminating negative feedback circuits. This may have implications for the level of the ST.

5. Aims and outline of this thesis

In summary, during the procedure of ECT, progressively large enough groups of cortico-(thalamo-)cortical connected neurons, embedded in supportive glia cells, fire synchronously, which leads to generalized seizure activity in (certain parts of) the brain. Scalp, skull, blood vessels, CSF, glia cells, damaged connections between brain tissue and inhibitory feed-back systems have all been suggested to hamper this process. To our knowledge, studies are lacking, which relate ST and effectiveness of ECT to anatomical factors (e.g., thickness of scalp and skull, volumes of gray matter, white matter, and CSF), as barriers for the current to reach the brain effectively. Also, studies relating ST and effectiveness of ECT to cerebral pathology (e.g., white matter hyperintensities, cortical atrophy), as determinants of the integrity of neuronal networks, which may hamper seizure propagation and/or termination, are not yet available. This thesis outlines studies that explore predictors of ST and its increase during the course in patients undergoing ECT.

The aims of our study in **Part 1** are to explore levels of IST in patients undergoing ECT and to examine clinical and anatomical determinants of the ST. In *Chapter 2* we describe the results of a meta-analysis of studies providing IST levels to determine common levels of IST in patients and to summarize its reported determinants. In *Chapter 3*, we study a patient with an exceptionally high IST and we systematically review the literature on this phenomenon, paying special attention to clinical and treatment characteristics as determinants of the IST. We also describe strategies for the management of high IST. *Chapter 4* contains a systematic literature review on hypotheses regarding clinical, morphological and functional determinants of changes in ST in older patients.

In **Part 2**, we examine in a prospective, explorative cohort study the hypothesized determinants of IST as described in Part 1 of this thesis. *Chapter 5* reports on the clinical characteristics influencing IST and ST change during the course of ECT. Correcting for the clinical variables influencing IST independently, *Chapter 6* examines the relation between scalp and skull thickness and structural brain characteristics (volumes of CSF, gray matter, white matter and white matter hyperintensities) related to IST and ST change during the course.

Part 3 of this thesis deals with the patients themselves. *Chapter 7* reports on our prospective study regarding clinical, treatment and morphological predictors of outcome in ECT. Furthermore, catatonic patients are retrospectively examined regarding ECT characteristics (seizure length, used electrical dosage and post-ictal suppression of the EEG) and outcome (*Chapter 8*). In *Chapter 9*, we study retrospectively

the relationship between time-interval between sessions, electrical dose and seizure duration, in patients treated with continuation ECT because of treatment-resistant mood disorder.

In conclusion, *Chapter 10* presents a summary and general discussion of the overall results, limitations, and the implications of our studies for clinical practice and further research.

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